Psychiatry Research: Neuroimaging 276 (2018) 33–40

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Association between schizophrenia polygenic risk and neural correlates of emotion perception

Ilvana Dzafic[a,b,*], Hana Burianová[b,c], Sathish Periyasamy[a,d], Bryan Mowry[a,d]

[a] Queensland Brain Institute, University of Queensland, Brisbane, Australia
[b] Centre for Advanced Imaging, University of Queensland, Brisbane, Australia
[c] Department of Psychology, Swansea University, Swansea, United Kingdom
[d] Queensland Centre for Mental Health Research, Brisbane, Australia

ARTICLE INFO

Keywords:
Schizophrenia
Polygenic risk
FMRI
Dynamic emotion
Threat
Emotion regulation

ABSTRACT

The neural correlates of emotion perception have been shown to be significantly altered in schizophrenia (SCZ) patients as well as their healthy relatives, possibly reflecting genetic susceptibility to the disease. The aim of the study was to investigate the association between SCZ polygenic risk and brain activity whilst testing perception of multisensory, dynamic emotional stimuli. We created SCZ polygenic risk scores (PRS) for a sample of twenty-eight healthy individuals. The PRS was based on data from the Psychiatric Genomics Consortium and was used as a regressor score in the neuroimaging analysis. The results of a multivariate brain-behaviour analysis show that higher SCZ PRS are related to increased activity in brain regions critical for emotion during the perception of threatening (angry) emotions. These results suggest that individuals with higher SCZ PRS *over-activate* the neural correlates underlying emotion during perception of threat, perhaps due to an increased experience of fear or neural inefficiency in emotion-regulation areas. Moreover, over-recruitment of emotion regulation regions might function as a compensation to maintain normal emotion regulation during threat perception. If replicated in larger studies, these findings may have important implications for understanding the neurophysiological biomarkers relevant in SCZ.

1. Introduction

Schizophrenia (SCZ) is a highly debilitating and heritable mental illness, characterized by impairment in diverse abilities spanning perception, reasoning, and social cognition (de Jong et al., 2013; Green et al., 2004). Evidence suggests that the SCZ-related impairment in these abilities may be due to the dynamic interplay between genes and brain (Martin et al., 2014; Roffman et al., 2006). Current estimates from twin and family studies put the heritability of SCZ at 81% (Wahlstrom et al., 1986), which has led to large collaborative efforts to identify genes able to explain this heritability. However, to date, the identified genes explain only 7% of the liability to SCZ (Ripke et al., 2014). As SCZ is considered an umbrella term, likely encompassing a large number of aetiologies, one approach to explaining the missing heritability is to search for intermediate traits that lie on a causal pathway between the genotype and clinical phenotype. An endophenotype is described as an intermediate trait that theoretically should be measurable, heritable, and state-independent, with neurophysiological and neurocognitive qualities (Cannon and Keller, 2006; Mowry and Gratten, 2013). One of these neurocognitive intermediate traits is emotion perception, as it has well-established evidence of impairment and aberrant underlying brain function in SCZ (Namiki et al., 2007; Romero-Ferreiro et al., 2016; Vai et al., 2015). Robust evidence has emerged identifying emotion perception as a viable endophenotype for SCZ, as deficits in emotion perception are heritable, associated with SCZ risk genes, and apparent before illness onset (Bediou et al., 2007; Germine et al., 2016). It is thus of importance to investigate the specific processes and neurobiological underpinnings of emotion perception and their relationship with risk genes, as such research would lead to a clearer understanding of the pathway from genotype to clinical phenotype.

The endophenotypic role of emotion perception in schizophrenia has been highlighted with evidence of robust deficits in SCZ, which persist throughout the course of illness and which are also present in healthy individuals with high SCZ susceptibility (Behere, 2015). In a recent review, Behere (2015) posits that emotion recognition difficulties are trait markers for SCZ, particularly difficulties recognizing threatening emotions, such as anger, and misattribution of threat onto ambiguous facial expressions (Behere, 2015). Impaired threat processing was found to be a stable deficit, present in both acute and

* Corresponding author at: Queensland Brain Institute, University of Queensland, Brisbane, QLD 4072, Australia.
E-mail address: i.dzafic@uq.edu.au (I. Dzafic).

https://doi.org/10.1016/j.pscychresns.2018.04.005
Received 27 August 2017; Received in revised form 26 February 2018; Accepted 23 April 2018
Available online 25 April 2018
0925-4927/

remission phases of SCZ; however, these deficits were particularly heightened in those with psychotic symptoms. Thus, aberrant processing of facial expressions could potentially be linked to development of psychopathology. In support of this notion, a number of SCZ common genetic risk variants have been reported to be associated with emotion and facial processing ability and its underlying neural circuitry (Greenwood et al., 2011; Martin et al., 2014). Moreover, previous research investigating genetic susceptibility to SCZ has identified that healthy relatives of those with SCZ have impaired emotion perception, such as misattributing threat onto neutral expressions (Eack et al., 2010). In addition, research shows that healthy individuals with high SCZ risk have altered activity in emotion neural correlates, such as frontal regions, anterior cingulate gyrus, nucleus accumbens, amygdala, and hippocampus (Phillips and Seidman, 2008). Considering these abovementioned findings, in the current study we hypothesized that SCZ genetic risk in healthy individuals would be associated with aberrant brain processing during emotion perception, particularly for threatening emotions.

With large genome-wide association studies (GWAS) identifying over 100 common risk variants significantly associated with SCZ (Ripke et al., 2014), a new direction in the field has been to consider the polygenic nature of SCZ by quantifying the combined effect of variants into a polygenic risk score (PRS). Recently, a large polygenic study has shown that deficits in emotion recognition are significantly associated with SCZ polygenic risk across development, supporting the notion that impaired processing of facial expressions may constitute a link between genetic risk for SCZ and development of psychosis (Germine et al., 2016). Notwithstanding the important findings from this study, Germine and colleagues utilized emotion tasks with static pictures as stimuli, consequently examining different underlying mechanisms compared to naturalistic, dynamic displays of emotion (Arsalidou et al., 2011; Palumbo and Jellema, 2013). As the field is moving towards more ecologically valid tasks, it is important to assess emotion perception using dynamic, audio-visual displays in order to gauge real-life emotion processing. In addition, it may be important to evaluate different contexts of emotion recognition; for example, when a certain emotion is expected or unexpected. Recent evidence shows that individuals with SCZ have reduced precision in their prior expectations, which impairs perception (Adams et al., 2016); thus, it seems critical to explore the influence of SCZ genes on the underlying processes driving emotion perception impairment.

The impact of SCZ polygenic risk on emotion recognition has, thus far, been examined only at the behavioural level, with no study to date investigating the influence on brain function underlying emotion perception. As robust evidence highlights that SCZ is a disorder of aberrant brain function (Coyle et al., 2016; Liang et al., 2006), the objective of this study was to investigate the association between polygenic risk of SCZ in healthy individuals and the neural correlates of emotion perception. A recently new field of study, 'imaging genetics' has focused on the neurobiological intermediate traits of SCZ, informed by neuroimaging. Imaging genetics allows us to map the neural activity of abilities, such as emotion perception, as a function of genotype. Using the imaging genetics technique, a number of genome-wide significant risk variants have been investigated with respect to their association with the emotion brain network. The findings reveal that risk alleles of certain candidate genes are associated with increased and inefficient connectivity between frontal regions and limbic regions, which play a key role in emotion regulation and emotional learning (Curcic-Blake et al., 2012; Mothersill et al., 2013; Surguladze et al., 2012). As schizophrenia has a complex polygenetic architecture, recent imaging genetic studies have investigated the cumulative effects of risk variants (applying the polygenic risk model) on brain function (Birnbaum and Weinberger, 2013). Imaging polygenic studies have found associations between SCZ genetic risk and white matter volume (Terwisscha van Scheltinga et al., 2013), as well as neural inefficiency in frontal regions (Lancaster et al., 2016; Walton et al., 2013). However, no imaging genetic study to date has explored the association between polygenic risk of SCZ and the brain regions underlying emotion perception.

The objective of the current study was to investigate the association between polygenic risk of SCZ in healthy individuals and neural correlates of emotion perception, in different expectancy contexts. For this purpose, we used a previously validated Dynamic Emotion Perception (DEP) task (Dzafic et al., 2016), with increased ecological validity, three emotional conditions (anger, happiness, and neutral) expressed by an actor in an audio-visual video and two levels of expectation (congruency and incongruency with prior expectations). Our focus was on healthy individuals for the following reasons: (1) robust evidence shows that genetic risk for SCZ in healthy individuals influences emotion processing (Eack et al., 2010; Germine et al., 2016) and (2) healthy individuals present a cleaner sample, without the confounds of illness and medication, which affect brain function. For the polygenic risk scores (PRS) we used summary data from SCZ PGC2 (Ripke et al., 2014) to assess differences in brain activation during a functional magnetic resonance imaging (fMRI) scan. We conducted a multivariate analysis to characterize activity in brain regions that covaries with individual SCZ PRS during the DEP task. Based on the results of previous studies, we predicted that SCZ PRS would be associated with aberrant activity in neural correlates of emotion regulation and emotional learning (Curcic-Blake et al., 2012; Mothersill et al., 2013), such as frontal and limbic regions. Additionally, we predicted that schizophrenia PRS would have the strongest association with aberrant brain activity during the viewing of threatening emotions, as perception of these types of emotions is most impaired in schizophrenia (Behere, 2015) and healthy relatives of those with SCZ (Eack et al., 2010).

2. Methods

2.1. Participants

Twenty-eight Caucasian right-handed healthy controls (HC; mean age = 49.61, SD = 9.09, 18 male) were recruited from a population-based Australian sample. The ancestry of the sample was European. Screening was conducted over the phone prior to the recruitment, to confirm that participants had no history of eye disease, neurological disorders, metal implants, or current medication. The Mini International Neuropsychiatric Interview (M.I.N.I.) version 5.0.0 (Sheehan et al., 1998), was used to ensure that participants did not have current alcohol dependence and were not experiencing a major depressive episode. Intelligence quotient (IQ) was estimated using 2 subsets (vocabulary and matrix reasoning) of the Wechsler abbreviated scale of intelligence (WASI; Wechsler (1999). Participants were provided with an information sheet, which included a full description of the study and an MRI information sheet. Written informed consent was obtained. This research was approved by the West Moreton Hospital and Health Service, and The University of Queensland Human Research Ethics Committees.

2.2. Genotyping and quality control

Genotyping was conducted using Illumina OmniExpress-12 arrays containing >712,000 markers for 12 controls and PsychChip arrays containing >570,000 markers for 17 controls respectively. Standard quality control procedures for samples and markers were conducted using established protocols (Anderson et al., 2010). These two datasets were merged and single nucleotide polymorphisms (SNPs) were excluded if the minor allele frequency was <5%, if the call rate was <97%, or if the χ2-test for Hardy–Weinberg Equilibrium had a p-value < 1e−06. After filtering, 220,707 variants were used for PRS analysis.